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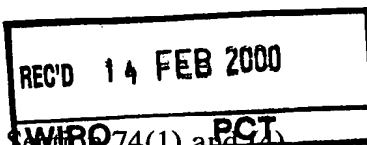
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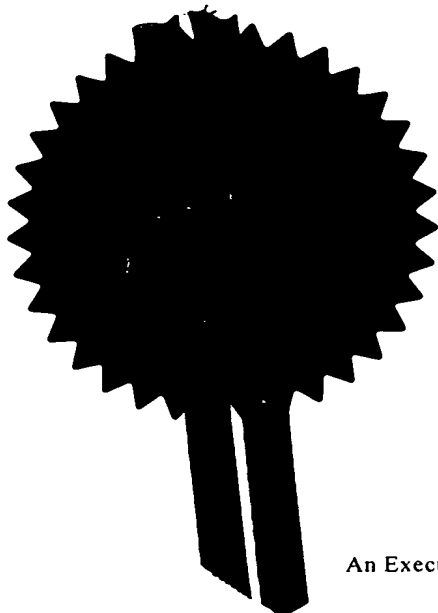
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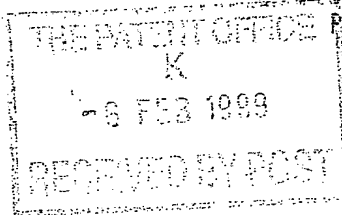
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1. Your reference

PHM 99-009

2. Patent application number

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06 FEB 1999

9902591.8

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Zeneca Limited
15 Stanhope Gate
LONDON W1Y 6LN
Great Britain

Patents ADP number (*if you know it*)

6254007002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

PHARMACEUTICAL COMPOSITIONS

5. Name of your agent (*if you have one*)

DENERLEY, Paul Millington

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

Intellectual Property Department
ZENECA Pharmaceuticals
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG
Great Britain

Patents ADP number (*if you know it*)

1030618002

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Number of earlier application

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Abstract

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

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11.

I/We request the grant of a patent on the basis of this application.

Signature

Lynda M. Slack Date 5th Feb 99
Zeneca Limited Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

Lynda M Slack 01625 516173

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PHARMACEUTICAL COMPOSITIONS

The present invention relates to a new use for (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the AGENT), in the improvement of diabetic neuropathy, specifically in improving neurone conduction velocity in patients suffering diabetes, in particular to pharmaceutical combinations of the AGENT and other agents known to improve diabetic neuropathy such as an aldose reductase inhibitor (ARI), an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II (AII) antagonist which combinations are useful in the prevention and treatment of the complications of diabetes mellitus.

Diabetes mellitus is a chronic disease characterised by hyperglycaemia and by complications that include diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic cataract and the like.

3-hydroxy-3-methylglutaryl Coenzyme A (HMG Co A) reductase inhibitors effectively inhibit cholesterol synthesis in the liver through stimulation of the low density lipoprotein (LDL) receptors. These drugs are currently pre-eminent in the treatment of all hypercholesterolaemia, except the relatively rarely occurring homozygous familial hypercholesterolaemia. Therapy with HMG Co A-reductase inhibitors may result in regression of atherosclerotic vascular lesions and several HMG Co A-reductase inhibitors have proven to reduce mortality. Various HMG Co A-reductase inhibitors are marketed, and are collectively referred to as 'statins'.

We have discovered that (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the AGENT), the calcium salt of which is shown in Fig. 1 below, produce an improvement in the neurone conductivity velocity (NCV) in an animal model of diabetic neuropathy. Therefore, the AGENT may be used to improve diabetic neuropathy, whether in type I or type II diabetes.

Therefore we present as a first feature of the invention a method for treating neuropathy in patients suffering from diabetes which comprises administration to the patient of the AGENT.

As a preferred Feature of the invention we present a method for improving neurone conductivity velocity in patients suffering diabetic neuropathy which comprises administration to the patient of the AGENT.

Further features of the invention include use of the AGENT in the preparation of a medicament for use in the treatment of any of the conditions mentioned above.

Preferably the AGENT is used at a dose of 5 to 80 mg per day.

The AGENT is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase). Preferably the calcium salt is used as illustrated in Figure 1.

It will be appreciated that the AGENT may be administered in accordance with the invention alongside other treatments used for treating diabetes or the complications of diabetes, such as neuropathy, nephropathy, retinopathy and cataracts. Examples of such treatments include insulin sensitising agents. Examples of insulin sensitising agents include, for example, troglitazone, rosiglitazone, pioglitazone and MCC-555.

Other treatments are known also to improve NCV in diabetic neuropathy and as such these represent preferred combinations of the invention. Examples of such treatments include aldose reductase inhibitors, ACE inhibitors and AII antagonists.

The use of aldose reductase inhibitors or ACE inhibitors in improving NCV and treating diabetic neuropathy is disclosed in PCT/GB98/01959. The use of AII antagonists in improving NCV and treating diabetic neuropathy is disclosed in WO93/20816.

Suitable aldose reductase inhibitors include, for example, epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509).

Suitable ACE inhibitors include, for example, benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, and cilazapril, or a pharmaceutically acceptable salt thereof. A preferred ACE inhibitor includes, for example, lisinopril.

Suitable AII antagonists include, for example, losartan, valsartan and candesartan.

Independent aspects of the present invention include a pharmaceutical combination which comprises any one of the named statin drugs identified above and any one of the named ACE inhibitors identified above, or anyone of the aldose reductase inhibitors identified above, or any one of the AII antagonists identified above. Accordingly, further independent aspects of the present invention include the following:

- (1) A pharmaceutical combination which comprises the AGENT and lisinopril;
and
- (2) A pharmaceutical combination which comprises the AGENT and candesartan.

The 'pharmaceutical combination' may be achieved by dosing each component drug of the combination to the patient separately in individual dosage forms administered together or sequentially. Alternatively the 'pharmaceutical combination' may be together in the same unit dosage form.

Therefore, as a further aspect of the invention we represent a pharmaceutical composition comprising a combination as described herein above together with a pharmaceutically acceptable carrier and/or diluent.

Independent aspects of the present invention include a pharmaceutical composition which comprises any one of the named the AGENTs identified above and any one of the named ACE inhibitors identified above, or anyone of the aldose reductase inhibitors identified above, or any one of the AII antagonists identified above together with a pharmaceutically acceptable carrier and/or diluent. Accordingly, further independent aspects of the present invention include the following:

- (1) A pharmaceutical composition which comprises the AGENT and lisinopril;
and
- (2) A pharmaceutical composition which comprises the AGENT and candesartan;
together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT and an ACE inhibitor (including any of the ACE inhibitors specifically named above, in particular lisinopril), together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT and an aldose reductase inhibitor (including any specifically named above), together with a pharmaceutically acceptable carrier and/or diluent.

The pharmaceutical compositions of the present invention may be administered in a standard manner for example by oral or parenteral administration, using conventional systemic dosage forms, such as a tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions, sterile injectable aqueous or oily solutions or suspensions. These dosage forms will include the necessary carrier material, excipient, lubricant, buffer, bulking agent, anti-oxidant, dispersant or the like.

In particular, compositions for oral administration are preferred.

The doses of the AGENT, an aldose reductase inhibitor, an AII antagonist and an ACE inhibitor which can be administered in accordance with the present invention depends on several factors, for example the age, weight and the severity of the condition under treatment, as well as the route of administration, dosage form and regimen and the desired result, and additionally the potency of the AGENT, aldose reductase inhibitor, AII antagonist and ACE inhibitor employed in the composition. In addition, account should be taken of the recommended maximum daily dosages for the ACE inhibitors.

Prolonged administration of an ACE inhibitor at a therapeutically effective dose may be deleterious or give rise to side effects in certain patients, for example it may lead to significant deterioration of renal function, induce hyperkalemia, neutropenia, angioneurotic oedema, rash or diarrhoea or give rise to a dry cough. Administration of an ARI may also give rise to deleterious effects or side effects at the dose required to inhibit the enzyme aldose reductase sufficiently to produce a significant beneficial therapeutic effect. The present invention lessens the problems associated with administration of an ARI or an ACE inhibitor alone and/or provides a means for obtaining a therapeutic effect which is significantly greater than that otherwise obtainable with the single agents when administered alone. Furthermore, diabetic complications involve a complex mechanism or number of mechanisms, which initiate a cascade of biochemical alterations that in turn lead to structural changes. These may result in a diverse patient population. The present invention therefore provides the additional advantage that it allows tailoring of treatment to the needs of a particular patient population.

A unit dosage formulation such as a tablet or capsule will usually contain, for example, from 1 mg to 100 mg of the AGENT, from 0.1 mg to 500 mg of an aldose reductase inhibitor, from 0.1 mg to 500 mg of an ACE inhibitor. Preferably a unit dose formulation will contain 5 to 80 mg of the AGENT, 0.1 to 100 mg of an aldose reductase inhibitor, 0.1 mg to 100 mg of an AII antagonist and 0.1 to 100 mg of an ACE inhibitor.

The present invention covers the pharmaceutical combination of (or product containing) the AGENT and an aldose reductase inhibitor, an AII antagonist or an ACE inhibitor for simultaneous, separate or sequential use in the treatment of diabetic complications. In one aspect of the present invention, the AGENT and the aldose reductase inhibitor or AII antagonist or ACE inhibitor is presented in admixture in one pharmaceutical dosage form. In another aspect, the present invention covers the administration of separate unit dosages of the AGENT and aldose reductase inhibitor or AII antagonist or ACE inhibitor in order to achieve the desired therapeutic effect. Such separate unit dosages may be administered concurrently or sequentially as determined by the clinician. The present invention also covers an agent for the treatment of diabetic complications comprising a pharmaceutically acceptable carrier and/or diluent and, as active agents, the AGENT and an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor in quantities producing a synergistic therapeutic effect.

In another aspect of the invention there is provided a combination of pharmaceutical compositions for combination therapy of diabetic complications, the combination consisting of a pharmaceutical composition comprising the AGENT and a pharmaceutical composition comprising an aldose reductase inhibitor or a pharmaceutical composition comprising an AII antagonist or a pharmaceutical composition comprising an ACE inhibitor. Particular diabetic complications include, for example, diabetic neuropathy, diabetic nephropathy and diabetic retinopathy, preferably the diabetic complication is diabetic neuropathy.

A further aspect of the present invention comprises the use of the AGENT and an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor in the preparation of a pharmaceutical composition for use in the treatment of diabetic complications.

A further aspect of the present invention is a method for treating diabetic complications (such as diabetic neuropathy, diabetic nephropathy or diabetic retinopathy, preferably diabetic neuropathy) wherein a therapeutically effective amount of the AGENT in

combination with an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor is administered systemically, such as orally or parenterally. Where the patient to be treated is normotensive, the ACE inhibitor or AII antagonist will preferably be administered in amounts below that required to cause a reduction in blood pressure. Where the patient to be treated is hypertensive, the ACE inhibitor or AII antagonist will preferably be used in amounts usually employed to treat hypertension.

The effect of a pharmaceutical composition of the present invention may be examined by using one or more of the published models of diabetic complications well known in the art. The pharmaceutical compositions of the present invention are particularly useful for the prevention of, reducing the development of, or reversal of, deficits in nerve function found in diabetic patients, and therefore particularly useful in the treatment of diabetic neuropathy. This may be demonstrated, for example, by measuring markers such as nerve conduction velocity, nerve amplitude, quantitative sensory testing, autonomic function testing and morphometric changes. Experimentally, studies analogous to those described in Diabetologia, 1992, Vol. 35, pages 12-18 and 1994, Vol. 37, pages 651-663 may be carried out.

A further aspect of the present invention is a method of treating or preventing the development of disease conditions associated with impaired neuronal conduction velocity in a warm-blooded animal (including a human being) requiring such treatment which comprises administering to said animal a therapeutically effective amount of a pharmaceutical combination or composition as described above.

A further aspect of the present invention is a method of reversing impaired neuronal conduction velocity in a warm-blooded animal (including a human being) requiring such treatment which comprises administering to said animal a therapeutically effective amount of a pharmaceutical combination or composition as described above.

Dosages of the Agent may be administered according to the cholesterol lowering effect desired from a range of 5-80 mg per day in any number of unit dosages. The dose ranges and dosages described above are further independent features of the invention.

The following non-limiting Examples serve to illustrate the present invention.

Example 1

	Capsule	mg
	The AGENT	5.0
5	Lactose	42.5
	Corn starch	20.0
	Microcrystalline cellulose	32.0
	Pregelatinised starch	3.3
	Hydrotalcite	1.1
10	Magnesium stearate	1.1

Capsules containing 1, 2.5 or 10mg of the AGENT may be obtained similarly using more or less lactose as appropriate., to achieve a fill weight of 105mg.

15	Tablet	mg
	The AGENT	10
	Polyvinylpyrrolidone	2.5
	Tricalcium phosphate	20
	microcrystalline cellulose	47
	Mannitol	47
	Sodium starch glycolate	3

Example 2

- 25 Suitable pharmaceutical compositions containing an the AGENT and an ACE inhibitor in a single dosage form include the following:

Tablet

	Tablet	mg
	ACE inhibitor~	10
5	The AGENT	10
	Polyvinylpyrrolidone	2.5
	Tricalcium phosphate	20
	microcrystalline cellulose	47
	Mannitol	47
10	Sodium starch glycolate	3

Example 3

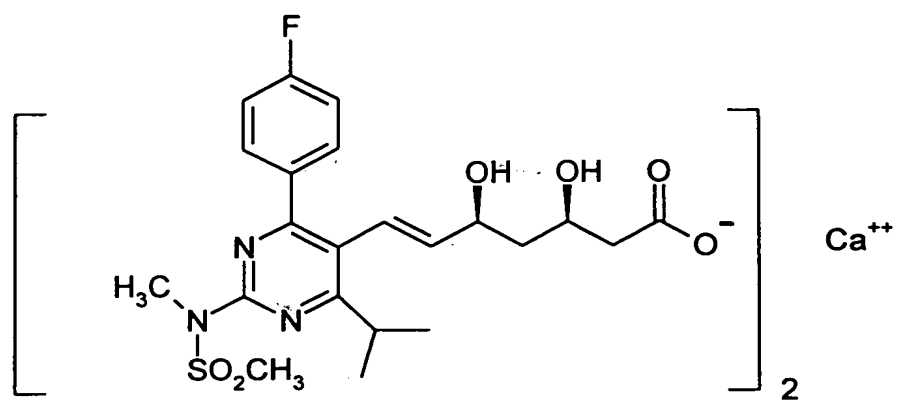
15 A patient requiring treatment for diabetic neuropathy is treated with the AGENT (10 mg) and lisinopril (10 mg). Lisinopril is administered twice daily and the AGENT is administered once daily.

Example 4

20 Male Sprague-Dawley rats, 19 weeks old at the start of the study, were divided into non-diabetic animals (normal control group) and animals rendered diabetic by intraperitoneal administration of streptozotocin, (40 - 45 mg/kg, freshly dissolved in sterile saline). Diabetes was verified 24 hours later by estimating hyperglycemia and glucosuria (Visidex II and Diastix; Ames, Slough, UK). Diabetic rats were tested weekly and weighed daily. Animals were rejected if the plasma glucose concentration was < 20 mM or if body weight
25 consistently increased over 3 days. Samples were taken from the tail vein or carotid artery after final experiments for plasma glucose determination (GOD-Perid method; Boehringer Mannheim, Mannheim, Germany). After 6 weeks of untreated diabetes, groups of rats were treated for a further 2 weeks with the AGENT, dissolved in the drinking water.

30 At the end of the treatment period, rats were anesthetized with thiobutabarbital by intraperitoneal injection (50 - 100 mg/kg). The trachea was cannulated for artificial ventilation and a carotid cannula was used to monitor mean systemic blood pressure. Motor

nerve conduction velocity was measured (as previously described by Cameron et al, Diabetologia, 1993, Vol. 36, pages 299-304) between sciatic notch and knee in the nerve branch to tibialis anterior muscle, which is representative of the whole sciatic nerve in terms of susceptibility to diabetes and treatment effects.



Formula I